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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,120	10/17/2001	Sanford M. Simon	600-1-280N	9363

23565 7590 09/23/2004

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,120	SIMON ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-53* is/are pending in the application.

4a) Of the above claim(s) *33-51 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 21-32, and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 7/9/04 has been entered. As previously noted in the last communication mailed to applicants on 6/29/04, the amendment and response, and the Declaration under 37 CFR 1.132 by Dr. Simon received on 4/16/04 have also been entered. Claim 20 has been canceled. Claims 1-19 and 21-53 are pending in the instant application. This application contains claims 33-51 and 53 drawn to an invention non-elected with traverse in applicant's submission dated 10/10/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-19, 21-32, and 52 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Nucleotide and/or Amino Acid Sequences

Applicant's submission of a sequence listing in paper form and CRF is acknowledged. Applicant's amendment of the specification on page 14, adding a SEQ ID NO. for the disclosed amino acid sequence is also acknowledged. This application is now in compliance with 37 CFR 1.821-1.825.

Claim Rejections - 35 USC § 101

The rejection of claims 1-16 and 52 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of applicant's amendment to the claims limiting the mammals to non-human mammals.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 10-11, 15-17, 26-27, and 31-32 under 35 U.S.C. 112, first paragraph, for lack of written description is withdrawn in view of applicant's amendments to the claims and arguments which indicate that the combination of detectable markers refers to two separate detectable markers, and further in view of applicant's support for fluorescence quenching proteins in the form of FRET pairs as disclosed in the specification.

The rejection of claims 1-16, and 52 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement for making and using genetically modified non-human mammals according to the instant invention other than transgenic mice is withdrawn in view of applicant's submission of supporting evidence in the form of publications which show that transgenic mammals capable of germline transmission of a transgene could be prepared by microinjection of pronuclei at the time of filing.

The rejection of claim 1-32 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendment to the claims. In particular, the applicant has clarified that the "a combination of an autofluorescent protein or peptide and an enzymatically-active protein or peptide" refers to two separate detectable markers and no a single protein which both autofluoresces and has enzymatic activity.

Applicant's claim amendments have resulted in new grounds of rejection under 35 U.S.C.112, second paragraph, see below.

Claims 1-19, and 21-32 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claims 1 and 17 have been amended to recite a genetically-modified non-human mammal or cell derived from said mammal containing a genetic construct comprising a polynucleotide sequence encoding an immunoglobulin and at least one detectable protein, wherein said construct comprises the CH1, CH2, and G1 exons spliced together to make the constant region of the secreted form of the immunoglobulin molecule, wherein said mammal is capable of expressing at least one chimeric immunoglobulin gene comprising a polynucleotide sequence encoding at least one detectable protein or peptide fused with a gene expressing an immunoglobulin component selected from the group consisting of the immunoglobulin kappa light chain, lambda light chain, or heavy chain. As amended, claims 1 and 19, and thus 2-18, and 21-32 which depend on claims 1 and 19, are confusing in that it is unclear whether the polynucleotide sequence which is expressed is the same

polynucleotide sequence contained in the construct. As written, the claims appear to be referring to two different polynucleotide sequences, one which encodes a heavy chain IgG1 immunoglobulin gene and a detectable protein, and a second which encodes and expresses any immunoglobulin light chain or heavy chain fused to a detectable protein. If the polynucleotide sequence in the construct and the polynucleotide sequence expressed are intended to be one and the same, then the limitations attributed to the expressed polynucleotide are in conflict with those of the polynucleotide in the genetic construct since the construct polynucleotide comprises immunoglobulin heavy chain sequences, particularly the CH1, CH2, and G1 heavy chain constant region exons, not kappa light chain or lambda light chain sequences, or other heavy chain gene sequences such as the IgM, IgD, or IgA constant region exons. Claims 2-5 are further confusing in that they refer to "said fusion polynucleotide" in claim 1. However, claim 1 recites two polynucleotides, neither of which are identified as a "fusion polynucleotide". Thus, it is unclear to which polynucleotide these claims refer. If the applicant does intend to claim cells and mammals comprising two different polynucleotides, it is suggested that the claims be amended to identify the first polynucleotide and the second polynucleotide.

Claim Rejections - 35 USC § 102

The rejection of claims 17-19 and 22-25 under 35 U.S.C. 102(b) as being anticipated by Fell et al. is maintained. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant has amended claims 17-19 and 22-25 such that the claims are now product by process claims. The applicant argues that Fell et al. teaches an *in vitro* method for producing genetically modified antibody producing cells and does not teach the *in vivo* method disclosed by applicants. In response, the applicant is reminded that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Thus, Fell et al. is not required to teach making the cells using the exact method used by applicants as long as the cells made are the same. In the instant case, Fell et al. teaches genetically modified antibody producing cells in which a component of an immunoglobulin gene has been replaced with a portion of the human variable or constant gene linked to an enzyme or substrate such as betagalactosidase, alkaline phosphatase, or horseradish peroxidase (Fell et al., column 11, lines 24-66, and column 12, lines 1-12). Fell et al. discloses that the antibodies produced by these cells are detectable and can be used as labeled antibodies in diagnostic assays without further modification (Fell et al., column 11). Fell et al. further teaches that the replacement gene can be inserted into either or both of the light chain or heavy chain immunoglobulin genes (Fell et al., column 10). In addition, Fell et al. teaches that the replacement gene can be linked to the C-terminus of the chimeric immunoglobulin (Fell et al., Figures 1B + 1C). Fell also teaches a specific embodiment where the replacement gene encodes all or a portion of IgG1, such that the linked enzyme is present in exon G1 (Fell eta l., column 14, lines 55-67). Thus, Fell et al. teaches

cells with the same structural and functional limitations as the cells recited in claims 17-19 and 22-25. As such, Fell et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The rejection of claims 20-21 and 27-30 under 35 U.S.C. 103(a) as being unpatentable over Fell et al. in view of Casey et al. is maintained over pending claims 21 and 27-30. Claim 20 has been canceled. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action contained two separate 103 rejections. However, it is noted that the applicant has not provided separate arguments for each rejection. The instant rejection is based on the teachings of Fell et al. in view of Casey et al. Applicant's arguments regarding the teachings of Fell et al. and Casey et al. have been addressed in relation to this rejection.

The applicant argues each reference separately and concludes that Fell et al. does not teach the making the cells in vivo as recited in claims as amended, or the various detectable proteins recited in dependent claim 27, and that Casey et al. also does not teach in vivo methods or the particular detectable proteins now claimed in claim 27. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231

USPQ 375 (Fed. Cir. 1986). Further, as noted above in the discussion of the rejection under 35 U.S.C. 102, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Thus, neither Fell et al. nor Casey et al. are required to teach making the cells using the exact method used by applicants as long as the cells made are the same.

The teachings of Fell et al. are discussed in detail above. Fell et al. teaches cells with all the limitations of the instant claimed cells except that Fell et al. doesn't teach using a flexible linker between the immunoglobulin and the detectable protein, and Fell et al. doesn't teach using an autofluorescent protein such as GFP as the detectable marker. However, the rejection of record cites Casey et al. for teaching the construction of detectable antibody by transfecting cells with a vector encoding a single chain antibody operably linked to a flexible glycine linker and GFP (Casey et al., page 446, Figure 1, construct iv). Please note that GFP is an autofluorescent protein and as such meets the claims limitations of claims 27-29. The fact that Casey et al. used bacterial cells to produce the antibody is not relevant, since Fell et al. provides the primary teaching for producing antibodies in mammalian cells. Further, Casey et al. was cited for providing motivation for substituting the flexible linker-GFP marker for the beta-galactosidase marker taught by Fell et al. by teaching that fluorescent labels provide high levels of sensitivity for a wide range of analytical assays (Casey et al., page 445). Thus, the skilled artisan would

have been motivated to substitute the nucleic acid sequence encoding the flexible linker-GFP taught by Casey et al. for the nucleic acid sequence encoding the beta-galactosidase detectable marker in the construct taught by Fell et al. based on the high level of sensitivity in detecting GFP and on the fact that fluorescent antibodies can be directly detected without the need to treat the cells or purified antibodies with additional reagents such as X-gal in the case of beta-galactosidase.

The applicant has not addressed the motivation provided by the office for combining the teachings of Fell et al. and Casey et al. The applicant instead argues that Fell et al. was published 14 years ago and that if it were obvious to combine the teachings of Fell et al. with Casey et al., someone would have done so prior to the filing of the instant application. In response to applicant's argument based upon the age of the references, contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977). Thus, applicant's arguments that the inventors were the first to appreciate the merits of making an antibody with a detectable GFP marker are not persuasive in view of the combined teachings of Fell et al. and Casey et al. Furthermore, the applicant is reminded that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Therefore, in view of the motivation to make a genetically modified chimeric

antibody linked to GFP as provided by Casey et al., it would have been *prima facie* obvious at the time of filing for the skilled artisan to replace the nucleic acid sequence encoding beta-galactosidase in the construct taught by Fell et al. with the nucleic acid sequence encoding the flexible linker/GFP taught by Casey et al. with a reasonable expectation of success.

The rejection of claims 1-9, 11-14, and 52 under 35 U.S.C. 103(a) as being unpatentable over Fell et al. in view of Casey et al. and Rajewsky et al. is maintained. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

As noted above, the applicant has not provided a separate set of arguments for this rejection. The arguments directed to the teachings of Fell et al. and Casey et al. have been addressed in detail above. In regards to the teachings of Rajewsky et al., the applicant sets forth the same argument applied to Fell et al., i.e. that Rajewsky et al. is 12 years old. Again, it is noted that contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977). The applicant further argues that Rajewsky et al. does not teach in vivo methods of generating detectable labeled antibodies . In response, it is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Fell et al. in view of Casey et al. were already cited for providing the teachings and motivation to make genetically modified cells capable of expressing

detectably labeled antibodies comprising various detectable markers including enzymatically active marker proteins and fluorescent marker proteins. The previous office action stated that Fell et al. in view of Casey et al. differ from the instant claims in that neither teach making a genetically modified mammal to express the chimeric labeled antibodies. Rajewsky et al. was cited for providing motivation for making transgenic mammals to produce chimeric antibodies *in vivo* over the *in vitro* methods of producing antibodies taught by Fell et al. Rajewsky et al. is not required to teach making detectable antibodies since that teaching has already been provided by Fell et al. Rajewsky et al. teaches methods of making transgenic mammals comprising genetically modified chimeric immunoglobulin and provides specific motivation for producing chimeric antibodies *in vivo* over *in vitro* methods based on the drawbacks to in vitro methods of antibody production including the cumbersome work required to generate specific monoclonal antibody of appropriate biological function and the difficulty in producing large quantities of these antibodies (Rajewsky et al., column 1). Rajewsky et al. teaches that the use of transgenic mice overcomes these obstacles since every cell possesses the inserted replacement gene such that exposure to different antigens will produce chimeric antigen-specific antibodies in quantities substantially larger than the amount capable of being expressed by cells in tissue culture. Therefore, based on the benefits of producing chimeric antibodies using transgenic mice over recombinant cells in tissue culture, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the homologous recombination vector taught by Fell et al. to produce transgenic mice according to the methodology taught by Rajewsky et al.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER